AMENDMENT

In the Claims

Please cancel claim 5 without prejudice.

Please amend claims 1 and 2 as indicated below:

1. (Amended) A monoclonal antibody having specificity to a LAR phosphatase subunit.

2. (Amended) A monoclonal antibody having specificity to an intracellular domain of a LAR phosphatase subunit.

REMARKS

I. PRELIMINARY REMARKS

The Applicants thank the Examiner for the telephonic interview (*see* Interview Summary filed August 30, 2002), in which the Examiner indicated that the outstanding Office Action is a non-final action. The Applicants also call to the Examiner's attention co-owned and co-pending U.S. patent application number 09/743,492 (Attorney Docket No. 19036/37023), which has been listed along with other documents on an enclosed Supplemental Information Disclosure Statement (IDS).

II. PROSECUTION HISTORY

The application as filed contained thirty-nine claims. In a preliminary amendment dated December 8, 2000, the Applicants amended claims 4-7, 10, 12-13, 15, 16, 19, 20, 22, 24, 26, 28, 29, 32, 33, 35 ,36, 38, and 39, and amended the Sequence Listing to comply with USPTO format requirements (37 C.F.R. § 1.821) without introducing new matter. In a second preliminary amendment dated January 10, 2001, the Applicants amended claim 39. In an amendment dated May 20, 2002, the Applicants amended claims 4 and 6. In the Office Action, the Examiner allowed claims 3, 11, 14 and 16-18, withdrew all rejections under 35 U.S.C. § 112, First and Second paragraphs, and 35 U.S.C. § 103(a), and rejected claims 1, 2, 4-10, 12, 13, 15, 19, 27 and 28 under 35 U.S.C. § 102(b).

III. EXPLANATION OF AMENDMENTS

A marked-up version of the changes made to the claims can be found in Appendix A hereto. Support for the amended claims is found throughout the specification. *See, e.g.*, pages 38-43 of the specification. As a convenience to the Examiner, the Applicants

have set forth in Appendix B all claims that will be pending after entry of the foregoing amendment. The Applicants do not intend by these or any other amendments to abandon the subject matter of any claim as originally filed or later presented, and reserve the right to pursue such subject matter in related applications.

IV. THE REJECTIONS UNDER 35 U.S.C. § 102(B) SHOULD BE WITHDRAWN

A. Rejection Based on Streuli, *et al.*

In paragraph 6 of the Office Action, the Examiner rejected claims 1, 4-6, 12, 13, 15, 19, 27, and 28 asserting that these claims were anticipated under 35 U.S.C. § 102(b) over Streuli, *et al.*, *EMBO Journal* **11**:897-907 (1992) (hereafter "Streuli, *et al.*, (1992)"). The Applicants traverse this rejection.

The rejection is based in part on the assertion that the Applicants have not indicated what "specificity" means. However, in the paragraph beginning on page 6, line 21, the specification recites: "[t]herefore, it was also necessary to produce antibodies which are specific to a LAR intracellular domain but not to CD45." The antibodies of the present application are specific to LAR phosphatase subunits, **and thus not cross-reactive with CD45 phosphatase subunits**.

The Examiner also stated that the "Streuli reference teaches an antibody that binds to a LAR protein (150 kDa designated the LAR extracellular or E-subunit) with the same molecular weight as the instant invention." The Examiner concluded that the antibody(ies) taught by Streuli *et al.* anticipates the invention as claimed because Streuli *et al.* apparently teaches an antibody that binds to a LAR subunit that possesses the same molecular weight as an antibody of the present application, and because Streuli *et al.* assertedly teaches that this subunit is linked to medullary thyroid cancer.

In response, Applicants submit that Streuli, *et al.* does not teach an antibody that specifically binds to the phosphatase subunit of LAR, as recited in the pending claims. Streuli *et al.* disclose that the extracellular-, or E-, subunit of LAR is "composed of three Ig domains and eight FN-III domains." (*See* p. 898, Col. 1.) Streuli *et al.*, then disclose that "antibodies that bound only to LAR were specific to the LAR FN III domains." (*Id.* at Col. 2.) In Fig. 1 of Streuli *et al.*, a schematic illustration of LAR is provided. That schematic illustrates the eight FN III domains of the E-subunit as small hatched boxes. That same Figure reveals that there are no such domains in the phosphatase, or P-, subunit. In addition to LAR-specific monoclonal antibodies, Streuli *et al.* disclosed "mAbs," or monoclonal

antibodies, that specifically recognized both a LAR-LCA hybrid, or fusion, protein and LAR. (*See* p. 898, Col. 2.) With respect to this less specific class of antibody, Streuli *et al.* stated that "mAbs that bound to both the LAR-LCA hybrid and LAR were specific to the LAR Ig domains." (*Id.*) Again referring to Fig. 1 of Streuli *et al.*, the Ig domain is schematically illustrated as a loop structure. Consistent with the text, the E-subunit of LAR is shown to have three Ig domains. The P-subunit, in contrast, is shown to lack any Ig domain. Therefore, the antibodies of Streuli *et al.* that are taught as being specific for LAR are, in fact, specific for the FN III domains of the E-subunit and do not bind to the P-subunit. The antibodies of Streuli *et al.* that are taught as being specific to both the LAR-LCA hybrid and to LAR are, in fact, specific to the Ig domains of the E-subunit and do not bind to the P-subunit. The reasonable explanation for the apparent presence of the P-subunit in some of the figures of Streuli *et al.* showing results of immunoprecipitation studies is stated in the reference itself: "the precursor LAR protein is intracellularly cleaved into two subunits that remain associated as a heterodimeric structure . . . ." (*See* p. 901, Col. 1.) Thus, the disclosed immunoprecipitations involve antibody-mediated precipitation of the E-subunit, which may bring the P-subunit with it. Such indirect precipitation, however, does not show an antibody specific for the P-subunit itself. Based on the foregoing analysis, the Applicants submit that Streuli *et al.* does not disclose, expressly or inherently, the claimed subject matter drawn to a monoclonal antibody having specificity to a LAR phosphatase subunit.

Applicants further submit that statements in the Office Action relating to 150 kDa proteins were based on the reported size of an antigen, not an antibody. Streuli, *et al.* teach antibodies specific for a 150 kDa antigen, which is the E-subunit of LAR. While claim 12 does have a 150 kDa size limitation, this limitation in claim 12 refers to the size of the antibody itself, and not the antigen to which it binds.

Additionally, the Examiner asserted that Streuli, *et al.* teach that LAR, or a subunit of LAR, is connected to medullary thyroid carcinoma. The Applicants respectfully disagree, and note that Streuli, *et al.* make no mention of medullary thyroid carcinoma. Thus, Streuli, *et al.* could not, and did not, disclose or suggest a link between LAR (or a subunit of LAR) and medullary thyroid cancer.

B. Rejection Based on Asserted Admissions

In paragraph 8, the Examiner rejected claim 2 under 35 U.S.C. § 102(b) as assertedly being anticipated by Applicants' "admission" on page 6, lines 21-24 of the

specification. Specifically, the Examiner asserted that because the specification discloses a known antibody generated by Transduction Laboratories from a peptide having 196 amino acid residues that span the transmembrane region of CD45 and part of phosphatase domain I of CD45, the specification anticipates the invention as claimed. The Applicants traverse.

The claimed antibodies are specific to LAR phosphatase subunits and thus do not cross-react with CD45. The Transduction Laboratories antibody, in contrast, binds to CD45, as expressly noted in the statement in the specification upon which the Examiner is relying. In fact, the text in the specification following this statement establishes that the Transduction Laboratories antibody was not disclosed as specifically binding a LAR intracellular domain and not to CD45 and that, hence, a need remained in the art for the antibodies now claimed, which do exhibit such binding characteristics. Moreover, although both LAR and CD45 are actually classified as protein tyrosine phosphatases, the functions, expression, distribution and chemical structures of the two proteins are substantially different from one another. The present invention's monoclonal antibodies specific to LAR tyrosine phosphatase subunits are, thus, distinct from the Transduction Laboratories monoclonal antibody. Accordingly, the Transduction Laboratories antibody referenced in the specification does not anticipate the present invention, and the rejection should be withdrawn.

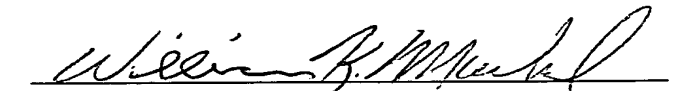
For all of the foregoing reasons, the Applicants respectfully submit that the rejections of claims 1, 2 and 4-6, 12, 13, 15, 19, 27, and 28 under 35 U.S.C. § 102(b) should be withdrawn.

SUMMARY

In view of the amendments and remarks made herein, the Applicants believe claims 1, 2, 4-10, 12, 13, 15, 19, 27, and 28 are in condition for allowance and request notification of the same.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By: 

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APPENDIX A

Version with markings to show changes made

Please amend claims 1 and 2 and cancel claim 5 as indicated below:

1. (Amended) [An] A monoclonal antibody having specificity to a LAR phosphatase subunit.

2. (Amended) [An] A monoclonal antibody having specificity to an intracellular domain of a LAR phosphatase subunit.

5. (Canceled)

APPENDIX B

Pending claims upon entry of the foregoing amendment

1. (Amended) A monoclonal antibody having specificity to a LAR phosphatase subunit.

2. (Amended) A monoclonal antibody having specificity to an intracellular domain of a LAR phosphatase subunit.

3. A monoclonal antibody having specificity to an intracellular domain of a LAR phosphatase subunit, and having no specificity to CD45.

4. (Twice Amended) The antibody according to claim 1, which is generated using a polypeptide encoded by a base sequence set out in SEQ ID NO: 1 as an antigen.

5. (Canceled)

6. (Twice Amended) The antibody according to claim 1 wherein the antibody is generated using a fusion protein comprising a LAR phosphatase domain and another protein as an immunogen.

7. (Amended) The antibody according to claim 1 wherein the antibody is generated using a GST-LAR phosphatase domain fusion protein as an immunogen.

8. The antibody according to claim 7 wherein the GST-LAR phosphatase domain fusion protein is produced by: culturing *Escherichia coli* transformed or transfected with an expression vector comprising a coding region of GST gene and a coding region of a phosphatase domain of LAR gene at 20-30°C for 16-24 hours; and isolating the fusion protein from the culture fluid and/or bacterial cells.

9. The antibody according to claim 8 wherein the GST-LAR phosphatase domain fusion protein is further purified based on an affinity to a support carrying glutathione wherein the elution of said fusion protein from the support is performed by boiling in the presence of a detergent.

10. (Amended) The antibody according to claim 6 wherein the antibody that was generated using the fusion protein as an immunogen is screened using said fusion protein.

11. A monoclonal antibody having specificity to a LAR phosphatase subunit, which is produced by a hybridoma with Accession No. FERM BP-6343.

12. (Amended) The antibody according to claim 5 having a molecular weight of about 150 kDa.

13. (Amended) A hybridoma cell line that produces the antibody according to claim 5.

14. A hybridoma cell line with Accession No. FERM BP-6343.

15. (Amended) A method for generating an antibody having specificity to a LAR phosphatase subunit, comprising a step of: immunizing an animal with a fusion protein comprising a LAR phosphatase domain and another protein or polypeptide fragment.

16. (Amended) A method for generating an antibody having specificity to a LAR phosphatase subunit, comprising a step of: immunizing an animal with a GST-LAR phosphatase domain fusion protein.

17. The method according to claim 16 wherein the GST-LAR phosphatase domain fusion protein is produced by: culturing Escherichia coli transformed or transfected with an expression vector comprising a coding region of GST gene and a coding region of a phosphatase domain of LAR gene at 20-30°C for 16-24 hours; and isolating the fusion protein from the culture fluid and/or bacterial cells.

18. The method according to claim 17 wherein the GST-LAR phosphatase domain fusion protein is further purified based on an affinity to a support carrying glutathione wherein the elution of said fusion protein from the support is performed by boiling in the presence of a detergent.

19. (Amended) The method according to claim 15, further comprising a step of: screening antibodies generated in the immunizing step using said fusion protein to identify an antibody having specificity to a LAR phosphatase subunit.

20. (Amended) A method of quantitative determination of LAR and/or LAR derived molecule comprising the step of: determining an amount of LAR protein and/or a fragment or a polypeptide that comprises at least a LAR intracellular domain, which is contained in a test sample using the antibody according to claim 1.

21. The method according to claim 20 wherein the antibody is used in any of immunobloting, immunoprecipitation and ELISA.

22. (Amended) A method for quantitative determination of LAR and/or LAR derived molecules comprising the steps of: isolating LAR and/or a fragment or a polypeptide that comprises at least a LAR intracellular domain, from a test sample using the antibody according to claim 1; and measuring an activity of the isolated LAR and/or LAR derived molecules.

23. The method according to claim 22 wherein affinity chromatography and/or immunoprecipitation by using a support that was bound with the antibody are utilized in the isolation step.

24. (Amended) A method for producing LAR and/or LAR derived molecules comprising the step of: isolating LAR protein and/or a fragment or a polypeptide that comprises at least a LAR intracellular domain using the antibody according to claim 1.

25. The method according to claim 24 wherein affinity chromatography and/or immunoprecipitation by using a support that was bound with the antibody are utilized in the isolation step.

26. (Amended) A method for identifying the presence of LAR and/or LAR derived molecules within tissue comprising the steps of: performing immunohistological examination using the antibody according to claim 1 to detect LAR protein and/or a fragment or a polypeptide that comprises at least a LAR intracellular domain.

27. An anti-LAR antibody having specific immunoreactivity to thyroid carcinoma cells.

28. (Amended) The antibody according to claim 1 having specific immunoreactivity to thyroid carcinoma cells.

29. (Amended) A method for diagnosis of thyroid carcinoma comprising the steps of: taking a thyroid tissue specimen from a subject suspected as suffering from thyroid cancer; and conducting diagnosis of thyroid cancer through evaluating immunoreactivity between the antibody according to claim 27 and said tissue specimen.

30. The method according to claim 29, wherein the thyroid tissue specimen is a specimen that is taken by fine needle aspiration, and the immunoreactivity is evaluated by an immunoassay.

31. The method according to claim 29 wherein the thyroid tissue specimen is a thyroid tissue section, and the immunoreactivity is evaluated by histological staining.

32. (Amended) A composition for histological diagnosis of thyroid carcinoma comprising the antibody to claim 27.

33. (Amended) A DDS formulation that was targeted to thyroid carcinoma cells using the antibody according to claim 27.

34. The DDS formulation according to claim 33 comprising one or more materials which are selected from the group consisting of nucleic acid, iodine, radioactive iodine, technetium and a protein.

35. (Amended) The DDS formulation according to claim 33 which is a pharmaceutical composition for diagnosis of thyroid carcinoma.

36. (Amended) The DDS formulation according to claim 33 which is a pharmaceutical composition for therapy of thyroid carcinoma.

37. The DDS formulation according to claim 36 further comprising an anticancer agent.

38. (Amended) The DDS formulation according to claim 36 wherein the nucleic acid is an antisense nucleic acid or a ribozyme.

39. (Twice Amended) A method for diagnosis of thyroid carcinoma comprising the steps: measuring an expression level of LAR mRNA from thyroid tissue of a subject suspected of suffering from a thyroid carcinoma, and diagnosing the presence or absence of thyroid carcinoma from the expression level of LAR mRNA.